National Institutes of Health
National Heart, Lung, and Blood Institute

RECOMMENDATIONS ON THE USE OF HYDROXYUREA THERAPY IN SICKLE CELL DISEASE

REVISED DRAFT
November 17, 2010

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DESCRIPTION OF THE GUIDELINE DEVELOPMENT PROCESS

During the development of these draft hydroxyurea guidelines, measures were taken to ensure the transparency of the evidence review process and to manage all potential or perceived conflicts of interest. During the invitation process, potential panel members were asked to disclose possible interests and relationships that could influence their participation as expert panel members. All panel members served as volunteers and were not compensated by the NHLBI or any other entity for their participation. An independent methodologist guided preparation of tables and a summary of the body of evidence for the panel's deliberation. The draft hydroxyurea guidelines were then reviewed by a panel of end-users for their feedback prior to public review. The draft hydroxyurea guidelines are being posted on the National Heart, Lung, and Blood Institute's Web Site for public review and comment before they are finalized. The hydroxyurea recommendations constitute one of five chapters of recommendations for the care of people who have sickle cell disease.

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INTRODUCTION

Sickle cell disease (SCD) is a group of inherited hemoglobin disorders characterized by a predominance of sickle hemoglobin (HbS) within the erythrocytes. Genotypes include homozygous hemoglobin SS and compound heterozygous conditions, such as hemoglobin S/β^0-thalassemia, hemoglobin S/β^+-thalassemia, and hemoglobin SC. The most common type of sickle cell disease is hemoglobin SS, which is commonly identified as sickle cell anemia. Patients who have hemoglobin SS and hemoglobin S/β^0-thalassemia have similar clinical findings. Thus, for the purposes of this discussion, both genotypes are considered sickle cell anemia.

Phenotypic variability among patients who have SCD is substantial and not solely accounted for by differences in genotype (Chui and Dover 2001). The clinical manifestations of SCD are numerous and diverse; they include pain, hemolytic anemia, and organ injury due to vaso-occlusion and vasculopathy. However, research shows substantial increases in survival and an increasing number of adults living with SCD. These trends are the result of effective newborn screening programs and enrollment of infants and children into comprehensive medical care programs that deliver proven preventive interventions (Quinn et al. 2010).

Currently, in the United States, no national guidelines exist for the care of patients who have SCD. Managing these patients' care can be complex, and the rarity of the disease often makes it difficult to find knowledgeable care providers. To assist patients, families, and care providers and ensure that all affected individuals receive high-quality care for SCD, the National Heart, Lung, and Blood Institute (NHLBI) has begun a process to develop national evidence-based guidelines for the management and treatment of SCD. These guidelines will assist providers with common management issues, including routine health maintenance; the treatment of both

acute and chronic complications of SCD; and the indications for, and the monitoring of, hydroxyurea and transfusion therapy.

This focused, evidence-based review of hydroxyurea therapy is the first in a group of systematic reviews of the available English-language evidence to develop recommendations for the management of patients who have SCD. The completed document will provide specific clinical guideline recommendations related to the most common acute and chronic complications and co-morbidities that affect people who have SCD. The document also will include recommendations for children.

The current document addresses the use of hydroxyurea in adults who have sickle cell anemia with moderate to severe clinical manifestations. A corresponding Evidence Report that informed the recommendations in this document is available on the National Heart, Lung, and Blood Web site and is included in the public comment process.

The all-volunteer Expert Panel is composed of health care professionals selected by NHLBI leadership. Panel members work with people and families affected by SCD. The panel includes experts in the areas of primary care, hematology, pediatric hematology, psychiatry, transfusion medicine, obstetrics/gynecology, and emergency department care. The panel is supported by a team from the Mayo Knowledge and Encounter Research Unit (Mayo-KER).

The Expert Panel is in the process of developing a comprehensive set of guidelines that will be made available for public comment in 2011. The panel will incorporate public comments during the development of the final SCD guidelines document, which will be issued in mid-2011.

BACKGROUND AND HISTORICAL PERSPECTIVE

This document focuses on the manifestations most relevant to the intervention of hydroxyurea therapy. Pain is the most common symptom of SCD. Pain can be acute, chronic, or of new onset superimposed on chronic symptoms. Smith and his colleagues (Smith et al. 2008) collected daily diaries for 232 adult patients; pain was reported on 54.5 percent of the more than 30,000 days analyzed. Patients sought medical care for pain on only 3.5 percent of those days. These data suggest that many patients who have SCD may be under-treated for their pain, may not perceive a benefit of treatment, or may have learned to self-manage their pain.

Understanding of the processes that lead to an acute vaso-occlusive crisis and the pathophysiology of the chronic pain syndrome remains limited. Rigid erythrocytes obstruct the microvasculature. A full understanding of how these events start and what role other factors—such as vascular adhesion molecules, leukocytes, reticulocytes, endothelial cells, and platelets—play in this process has not been fully elucidated. With the exception of the joint pain of avascular necrosis, chronic pain syndromes in SCD have not been studied. In other chronic pain syndromes, central sensitization is thought to play a role. Central sensitization is an abnormal responsiveness that produces pain hypersensitivity in noninflamed tissue and increased pain sensitivity after an initiating cause has disappeared (Latremoliere and Woolf 2009). Hsieh and his colleagues described four patients on chronic daily opioid medications for sickle cell pain who were weaned off of these medications after successful stem cell transplants (Hsieh 2009). This suggests the possibility that a reversible process may be responsible for the chronic pain that so frequently occurs in SCD.

Pulmonary complications are common in SCD. One of the most serious problems is acute chest syndrome (ACS), which often follows an acute vaso-occlusive crisis. The manifestations of ACS include fever, chest pain, hypoxemia, cough and/or dyspnea, and a new infiltrate evident on chest x ray involving at least one lung segment (Vichinsky et al. 2000). The multiple potential etiologies include infection, bone marrow fat embolization, and *in situ* sickling with pulmonary infarction. ACS causes significant morbidity and is associated with higher risk of death.

Multiple genetic and environmental factors influence the degree of hemolysis and the occurrence of vaso-occlusion in SCD. One of the best examples is the profoundly favorable effect that high fetal hemoglobin (HbF) levels have on preventing intra-erythrocytic hemoglobin S polymerization and vaso-occlusion. The beneficial effects of genetically determined, persistent elevations of HbF levels in patients who have SCD throughout their lifespan were documented through carefully conducted cohort studies in the 1970s and 1980s (Powars et al. 1984; Platt et al. 1991). These observations supported the concept that therapeutic interventions to increase HbF levels could improve clinical outcomes in patients who have SCD. 5-azacytidine was found to be capable of inducing HbF production in cell cultures, an effect confirmed in an animal model (DeSimone et al. 1982) and a few patients who had thalassemia or SCD. Other drugs capable of increasing HbF levels were sought to permit oral administration and more acceptable toxicity profiles.

Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as a promising candidate. This medication has been in use since the 1980s to treat patients who have myeloproliferative disorders. Hydroxyurea is known to have rapid absorption and near-complete bioavailability, and to be therapeutic with once-daily oral dosing. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia involved two patients. The study showed that short-term

hydroxyurea therapy increased the number of HbF-containing reticulocytes and was not associated with short-term toxicities (Platt et al. 1984). This favorable result led to two carefully planned, extended studies involving hydroxyurea treatment for larger cohorts of patients who had sickle cell anemia. Both of these interventional trials demonstrated that hydroxyurea was well tolerated and increased HbF levels in the majority of patients (Rodgers et al. 1990; Charache et al. 1992). The results provided the necessary information to plan a major prospective Phase III clinical study (Charache et al., "Design of the Multicenter Study," 1995).

The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) was a randomized, double-blind, placebo-controlled trial involving 299 adults with sickle cell anemia who had experienced three or more pain crises in the previous year. The clinical end point of three or more documented pain crises was chosen because of earlier data documenting that patients who experience pain at that frequency had markedly lower survival rates (Platt 1991). Hydroxyurea therapy was demonstrated to reduce the frequency of painful episodes and ACS events, as well as the need for red blood cell transfusions and hospitalizations (Charache et al., "Effect of Hydroxyurea," 1995). The 1998 Food and Drug Administration approval of hydroxyurea for the treatment of adults who have clinically severe sickle cell anemia was based on the results of MSH.

Although HbF induction is the most powerful effect of hydroxyurea and provides the most direct benefit for patients who have SCD, additional mechanisms and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters their expression of adhesion molecules, all of which contribute to vaso-occlusion (Ware 2010). Hydroxyurea raises erythrocyte volume (higher mean corpuscular volume (MCV)) and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion. Nitric

oxide released directly from hydroxyurea metabolism may contribute to local vasodilation (King 2004). These data suggest additional mechanisms for the benefits of hydroxyurea therapy for SCD.

A 9-year followup analysis of MSH participants indicated a reduction in mortality for the group of patients who took hydroxyurea compared to those who did not take the medication (Steinberg et al. 2003). More recently, extension of the followup analysis to 17.5 years indicated continued safety and benefit of hydroxyurea, including reduced mortality (Steinberg et al. 2010). Results from another prospective clinical study of hydroxyurea therapy with 17-year followup analysis were recently published (Voskaridou et al. 2010). This prospective, nonrandomized study in Greece enrolled patients older than 16 years who had hemoglobin SS or HbS/β-thalassemia syndromes. Similar to the results of the MSH trial, the results from this study showed that hydroxyurea therapy reduced the frequency of painful episodes and ACS events, as well as the need for red blood cell transfusions and hospitalizations. Hydroxyurea therapy also significantly improved survival when compared to conventional therapy.

For infants, children, and adolescents who have sickle cell anemia, emerging data document both the safety and efficacy of hydroxyurea (Ware 2010). Prospective trials, several of which are funded by the National Institutes of Health (NIH), have shown improvements in laboratory parameters and decreased numbers of sickle-related clinical events. Long-term studies suggest sustained beneficial effects of hydroxyurea for young patients, without excessive myelotoxicity, deleterious effects on growth and development, altered fertility, or increased carcinogenicity.

For the purposes of these guidelines, the Expert Panel and methodology team reviewed comprehensive literature addressing both efficacy and harm.

METHODOLOGY

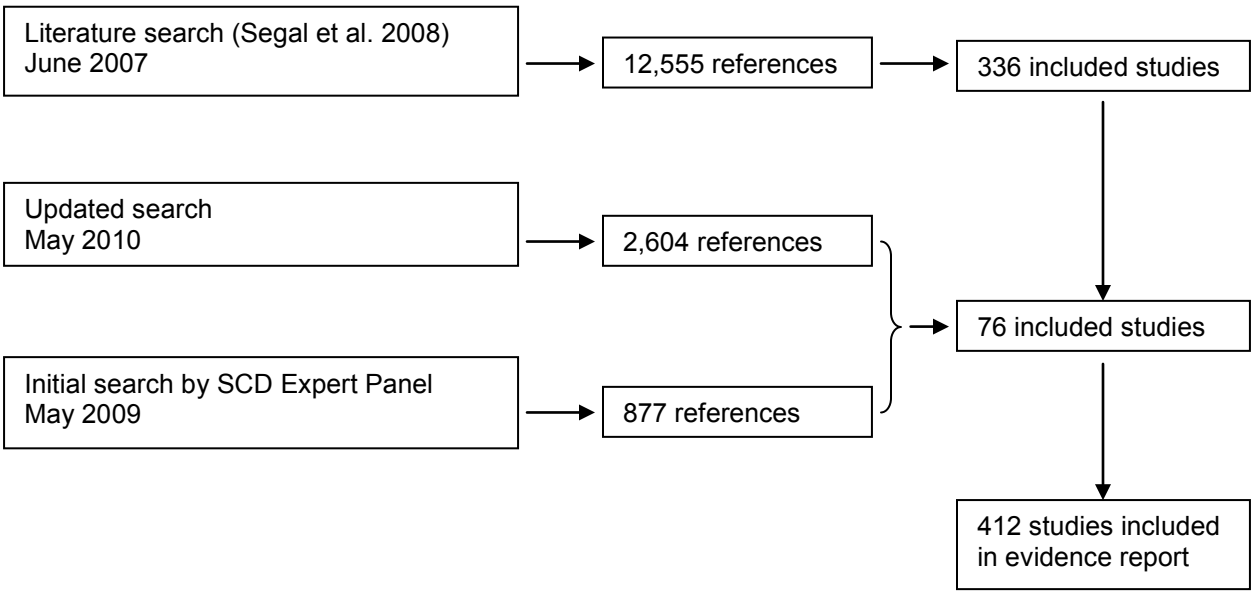
Starting in April 2010, the Expert Panel collaborated with the Mayo-KER methodology team to develop evidence-based clinical practice guidelines to evaluate the use of hydroxyurea in SCD. The Expert Panel identified the areas in which clinicians caring for patients who have SCD may need guidance, and they developed an initial set of potential recommendations that required literature searches and appraisals of evidence. A methodologist and an experienced librarian from Mayo-KER developed search questions and strategies and conducted the searches.

In addressing hydroxyurea therapy, recent well-conducted systematic reviews addressing both pediatric and adult patients were identified (Strouse et al. 2008; Lanzkron et al. 2008; Segal et al. 2008). The evidence center evaluated these reviews for the benefits, harms, and barriers of using hydroxyurea and updated the existing evidence base (Segal et al. 2008). The strategy used to conduct the systematic review was restricted to the English language and developed to capture nonrandomized studies because of the dearth of randomized trials in the field. Controlled vocabulary terms, supplemented with keywords, were used to define the concept areas: sickle cell disease, and the efficacy, effectiveness, barriers to use, and adverse effects of hydroxyurea. To update this systematic review, a comprehensive search of several databases (from 2007 to May 2010, English language, any population) was conducted. These included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, EBSCO Cumulative Index to Nursing and Allied Health Literature, TOXLINE, and Scopus. The search strategy is available in appendix B of the evidence report, which is titled “Hydroxyurea for Sickle Cell Disease: A Systematic Review of Benefits, Harms, and Barriers of Utilization.” The

Patient-Intervention-Comparison-Outcome (PICO) strategy is available in appendix A of this document.

As shown in exhibit 1, the original review search, done June 30, 2007, resulted in the retrieval of 12,555 references. The search was updated with 3 years of additional literature to render the body of evidence current and provide the Expert Panel with the accumulated knowledge to the present. The updated search resulted in 2,604 additional references. In addition, the Expert Panel had previously conducted an updated literature search that produced 877 references. The Mayo-KER team also reviewed and vetted these references based on the inclusion criteria.

Exhibit 1. Hydroxyurea Literature Search Process



Study selection and data extraction were conducted by pairs of reviewers working independently, until adequate agreement (kappa >=0.85) was obtained. At that point, the process was conducted by a single reviewer and verified by another. First, eligibility criteria were applied to titles and abstracts, and potentially eligible studies were retrieved in full text. Then eligibility criteria were applied to the full text document. Disagreements were noted and resolved by discussion and consensus among the Mayo-KER staff, erring on inclusion. Data extracted from each study

included description of enrolled patients, treatments, study quality measures, and outcomes. Both study selection and data extraction were conducted using sustainable procedures and a Web-based software (Distiller SR—http://systematic-review.net/). Meta-analysis was not feasible because only one randomized trial in adults was available, and the observational studies were heterogeneous and did not have sufficient data for quantitative analysis.

After the systematic review was conducted, the methodologists created evidence tables that describe the included studies and their findings; the tables also include evidence profiles that describe the quality of evidence. The Expert Panel reviewed the evidence and provided feedback and content expertise for the evidence profiles. In grading the recommendations, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was employed (Guyatt et al. 2008). GRADE is a state-of-the-art system to separately judge and report the quality of supporting evidence and the strength of the clinical recommendations. GRADE also allows for the incorporation of patients' values and preferences in the recommendations. Emphasis was placed on use of patient-important outcomes—those that affect the way patients feel, function, or survive (Gandhi et al. 2008)—over surrogate laboratory and physiologic outcomes.

When formulating final recommendations using the GRADE framework, the first step is to evaluate the quality of the evidence. The quality of evidence derived from randomized trials starts as "high," and the quality of evidence derived from observational studies starts as "low." The quality of evidence can then be lowered due to methodological limitations in individual studies, inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals),

and the presence of publication bias (assessed by inspecting funnel plots in meta-analyses). In the hydroxyurea chapter, there was only one randomized clinical trial, and the observational studies were heterogeneous. Thus, meta-analysis was not performed, and the presence of publication bias was not statistically evaluated. Conversely, the quality of evidence can be increased when the treatment effect is large, a dose-response relationship is evident, or the residual confounding is thought to strengthen the association (i.e., if the adjustment of confounding would result in a stronger association between the exposure and the outcome, the quality of evidence could be raised). After the consideration of these factors, the quality of evidence is rated as high, moderate, low, or very low.

The strength of recommendation (1 = strong, 2 = weak) was determined by (1) the quality of evidence, (2) the balance between desirable and undesirable effects, (3) values and preferences, and (4) resources and costs. The strength of the recommendation has important implications for clinicians. The benefits of an intervention clearly outweigh risks and burdens for grade 1 (strong) recommendations. All well-informed patients would choose such a treatment, and clinicians—often without detailed knowledge of the underlying data—can securely recommend it. Grade 2 (weak) recommendations reflect therapies in which the benefits and risks are either uncertain or more closely balanced. For such interventions, clinicians should be familiar with the evidence underlying the recommendation, and patients may choose different options based on their underlying values. Go to appendix B for a detailed description of how the Expert Panel used the GRADE framework to evaluate the recommendations.

Guideline developers consider what is known in the literature about patients' values and preferences and assume values demonstrated by patients encountered in clinical practice. In the area of SCD, the evidence supporting the nature and distribution of patients' values is not strong.

However, the Expert Panel has considered these values in their decisionmaking process. In one study of pediatric patients and their caregivers, preference was indicated for hydroxyurea over other therapies such as routine red blood cell transfusions or stem cell transplantation. The benefit/harm balance seems to be the driving determinant of treatment choice in this study (Hankins et al. 2007). In developing these recommendations, the Expert Panel placed high value on preventing SCD morbidity (specifically, pain crises and ACS) and low value on cost, burden, and potentially unknown adverse effects of hydroxyurea therapy. Although the clinical trials used very restrictive definitions regarding chronic, acute, and recurrent pain, the panel has chosen to broaden the definitions by using information from patients included in observational studies, as well information from patients in the clinical trials. It is the nature of efficacy clinical trials to severely restrict the group of patients included. Unfortunately, this limits data on the majority of patients who do not easily fit in to the restrictive clinical trial definitions—that is, the patients seen in everyday practice. Therefore, the panel's definitions of chronic, acute, and recurrent pain and recommendations for the use of hydroxyurea have been expanded in an effort to include the broad range of pain syndromes that affect sickle cell patients' ability to participate in their desired daily activities. The panel hopes to encourage use of the medication in patients who have acute and/or chronic pain that regularly interferes with their quality of life. For example, the panel deliberated extensively on using the clinical trials' data alone, which would limit the use of hydroxyurea to patients who have had three or more pain crises in the last year. However, the panel felt that this would prevent the use of hydroxyurea in some patients who have chronic, acute, and recurrent pain, and for whom observational studies have shown a possible benefit from the medication. In addition, when issuing recommendations for adult patients, the Expert Panel occasionally used data from the pediatric literature and also from

populations without SCD who were treated with hydroxyurea. This occurred particularly in the areas of harm and treatment initiation and monitoring. The panel acknowledges that this indirect evidence is of lower quality and associated with weaker inferences.

HYDROXYUREA TREATMENT RECOMMENDATIONS

Recommendations

1. In patients with sickle cell anemia who have **recurrent SCD-associated pain** that interferes with daily activities and quality of life, the Expert Panel recommends treatment with hydroxyurea (grade 1, high-quality evidence).

2. In patients with sickle cell anemia who have had **severe and/or recurrent acute chest syndrome** (for more information about ACS, go to page 4), the Expert Panel recommends hydroxyurea therapy (grade 1, moderate-quality evidence).

3. In patients with sickle cell anemia who have **severe symptomatic chronic anemia** that interferes with daily activities or quality of life, the Expert Panel recommends hydroxyurea therapy (grade 1, moderate-quality evidence).

4. The Expert Panel recommends that clinicians prescribing hydroxyurea follow an established prescribing and monitoring protocol to maximize benefits and safety, and to ensure proper use of hydroxyurea (grade 1, high-quality evidence).

(For more information, go to “Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy” on page 16.)

Summary of Evidence

1. Evidence of Efficacy/Effectiveness

A single randomized trial of 299 patients who had three or more pain crises a year at entry into the study (MSH) with followup analysis of 21 months demonstrated that compared to placebo, hydroxyurea treatment was associated with:

- Lower annual rates of pain crises (median, 2.5 versus 4.5 crises per year, P<0.001)
- Longer time to a first crisis (3.0 versus 1.5 months, P =0.01) and second crisis (8.8 versus 4.6 months, P<0.001)
- Lower incidence of ACS (25 versus 51 patients, P <0.001)
- Reduced need for blood transfusions (48 versus 73 patients, P=0.001)
- Increases in hemoglobin (0.6 g/dL) and HbF (from 5.0–8.6 percent in the intervention group, compared with a drop in the placebo group from 5.2–4.7 percent)
- Lower costs for hospitalization for pain ($12,160 in the hydroxyurea group versus $17,290 in the placebo group; P<0.05)

Differences in the effect on mortality and stroke outcomes were not statistically significant.

Over 2 years of treatment, the benefit of hydroxyurea treatment on quality-of-life measures was limited to patients who maintained a high HbF response. These restricted benefits occurred in social function, pain recall, and general health perception. Annualized total costs were similar between the intervention group and the placebo group. When the cohort was followed for up to

9 years, patients taking hydroxyurea had 40 percent reduced mortality (analysis according to cumulative hydroxyurea exposure, not the original randomization). Survival was related to HbF levels and frequency of vaso-occlusive events. The trial had adequate bias protection measures but was stopped early for benefit, which may exaggerate the observed benefit.

Supporting evidence from 21 observational studies with followup periods of 24–96 months was consistent in showing a reduction in pain crises (60–90 percent) and hospitalizations (90–100 percent) and an increase in HbF (4–20 percent). Both stopping early and imprecision (single trial with <300 events) of the randomized trial can affect the quality of evidence. However, overall the quality is considered high because the supporting observational evidence, the large treatment effect, and the change in disease trajectory that follows administration of hydroxyurea strengthen inference.

Exhibit 2. Evidence Profile—Evidence of Efficacy/Effectiveness

Outcome	Quality of the Evidence	Treatment Effect
Pain crises	High	Statistically significant benefit
Acute chest syndrome	Moderate	Statistically significant benefit
Need for blood transfusions, hemoglobin and fetal hemoglobin levels	High	Statistically significant benefit
Mortality	Very low	Imprecise estimate
Stroke	Very low	Imprecise estimate

Pico questions associated with this evidence profile include adult patients for whom SCD intervention is hydroxyurea, and comparison is usual care.

2. Evidence of Harm

The evidence of hydroxyurea toxicity in patients who have SCD is derived from two randomized controlled trials that enrolled 324 patients and 47 observational studies that enrolled over 3,000 patients. In patients who do not have SCD, toxicity evidence is derived from 21 randomized controlled trials that enrolled over 4,800 patients and 35 observational studies that enrolled over 7,500 patients.

Exhibit 3. Evidence Profile—Evidence of Harm

Potential Toxicity	Quality of the Evidence	Treatment Effect
Bone marrow suppression	High	Reversible neutropenia associated with hydroxyurea.
Leukemia	Low	The available evidence does not support association of hydroxyurea treatment with leukemia in adults or children who have SCD.
Leg ulcers	Adults: Moderate Children: Low	The available evidence does not support association of hydroxyurea treatment with leg ulcers.
Other side effects	Very low	Numerous other side effects were reported in the literature with low frequency and none with certain causality.
Reproductive effects of hydroxyurea	Very low	Minimal human data exist on potential harmful reproductive effects of hydroxyurea in males and females.

3. Evidence Supporting Use of a Treatment Protocol

Although the literature does not offer evidence comparing different implementation protocols for hydroxyurea, the Expert Panel was concerned about inadequate dosing or poor monitoring if a protocol was not used. Hence, taking into account the aforementioned values and the high-quality evidence supporting the use of protocols for hydroxyurea, the Expert Panel issued a strong recommendation for adopting a standardized protocol to maximize benefits and safety and ensure proper use of hydroxyurea. A suggested protocol was developed by the Expert Panel based on (1) protocols used in the published clinical trials and observational studies, (2) indirect evidence derived from basic science and pharmacokinetics of hydroxyurea, and (3) consensus and expert opinion processes. The protocol contains several technical remarks and recommendations needed to implement hydroxyurea therapy safely and effectively, but should be considered as guidance and modified to fit an individual patient's clinical situation.

Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and mean corpuscular volume (MCV)
- Quantitative measurement of HbF
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring[1]

- Any level of baseline elevation of HbF is not a contraindication to treatment.
- Both men and women of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease.
- Monitor CBC with WBC differential at least every 4 weeks when adjusting dosage.
- Maintain absolute neutrophil count ≥ 2,000/uL.
- Maintain platelet count ≥ 80,000/uL.
- If neutropenia or thrombocytopenia occurs:
  - Discontinue hydroxyurea.
  - Monitor CBC with WBC differential weekly.
  - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias.
- Monitor red blood cell MCV and HbF levels for evidence of laboratory response.

[1] Duration of therapy will be addressed in the full guidelines document.

- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
  - 5 mg/kg/day increments every 8 weeks.
  - Maximum of 35 mg/kg/day or until mild myelosuppression (ANC 2000–4000/uL) is achieved. This dose can be considered the maximum tolerated dose.
- Laboratory safety monitoring once a stable effective dose is established:
  - CBC with WBC differential and platelet count every 8 weeks.
- Patient should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a trial of 6 months on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure of response to therapy.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

Special Considerations

- In patients who have **chronic kidney disease**, the addition of hydroxyurea to recombinant erythropoietin may be considered to improve anemia.
- Patients receiving **red blood cell transfusions** on a monthly basis do not receive additional benefit from receiving hydroxyurea therapy.

- At this time, insufficient evidence exists regarding the use of hydroxyurea during pregnancy. The Expert Panel believes that until further evidence is available, **hydroxyurea should be discontinued during pregnancy and breastfeeding.**

GAPS IN RESEARCH

The Expert Panel's ability to make recommendations for several research areas was limited due to a lack of high-quality data. The following is a discussion of the research areas that the Expert Panel suggests the research community focus on to close these gaps. These suggestions have not been prioritized.

Data are needed concerning the efficacy of hydroxyurea in patients who have (1) genotypes other than hemoglobin SS and S/β^0-thalassemia, (2) less severe clinical manifestations, and (3) complications of SCD other than pain and severe anemia. More research also is needed on the long-term effects of hydroxyurea therapy on patients and on reproductive outcomes.

Data are needed concerning the barriers to optimal implementation of hydroxyurea therapy in the management of SCD in usual clinical settings. Specific concerns include the optimal frequency of laboratory testing for monitoring the safety of therapy; whether titrating the dose of drug is necessary to obtain maximal benefit; and the efficacy of hydroxyurea in combination with currently available interventions, such as red blood cell transfusions and erythropoietin, as well as novel therapies. A well-designed patient registry and prospective trials that examine the efficacy of hydroxyurea in patients who have a variety of clinical manifestations, at a maximally tolerated dose versus fixed dose and in combination with other therapies, could clarify these questions. A need also exists to address the efficacy of combination therapy with currently

available interventions, such as red blood cell transfusions and erythropoietin, as well as novel therapies.

Data are needed concerning the effects of hydroxyurea therapy during pregnancy. Studying these effects in both the mother and the fetus will help determine hydroxyurea's risks and benefits.

Data are needed concerning the barriers to the use of hydroxyurea and effective interventions to improve clinician and patient adherence to hydroxyurea therapy recommendations.

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APPENDIX A. PICO FORMAT FOR HYDROXYUREA SEARCH STRATEGY

Patients: Patients who have sickle cell disease (SCD)

Intervention: Hydroxyurea

Comparison: Usual care without hydroxyurea

Outcomes:

- Primary outcomes:
  - Benefits of hydroxyurea (death, stroke, pain crises, need for transfusion, hemoglobin and fetal hemoglobin levels)
  - Harms of hydroxyurea (adverse effects)
- Secondary outcomes:
  - Evaluate barriers to the implementation of hydroxyurea treatment
  - Evaluate the effectiveness of interventions to overcome barriers
  - Evaluate the effectiveness of different treatment protocols and monitoring parameters

Study Design for Hydroxyurea

Randomized or nonrandomized (for hydroxyurea harms, studies in patients who do not have SCD are included).

APPENDIX B. DETERMINING THE STRENGTH OF RECOMMENDATIONS

Exhibit B–1. Strong Recommendations

Rating of Evidence Quality	Clarity of Risk/Benefit	Description of Supporting Evidence	Implications
High quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed randomized controlled trials or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on our confidence in the estimate of effect and may change the estimate.
Low quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from randomized controlled	Recommendation may change when higher quality evidence becomes available. Further research is

Rating of Evidence Quality	Clarity of Risk/Benefit	Description of Supporting Evidence	Implications
		trials with serious flaws, or indirect evidence	very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.

1 Table modified from Schünemann H, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al. ATS Documents
2 Development and Implementation Committee. An official ATS statement: Grading the quality of evidence and
3 strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006
4 Sep 1;174(5):605–14.

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Exhibit B–2. Weak Recommendations

Rating of Evidence Quality	Clarity of Risk/Benefit	Description of Supporting Evidence	Implications
High quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed randomized controlled trials or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality evidence	Benefits closely balanced with harms and burdens	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality evidence	Uncertainty in the estimates of benefits, harms, and burdens;	Evidence for at least one critical outcome from observational	Other alternatives may be equally reasonable. Further research is

Rating of Evidence Quality	Clarity of Risk/Benefit	Description of Supporting Evidence	Implications
	benefits may be closely balanced with harms and burdens	studies, from randomized controlled trials with serious flaws, or indirect evidence	very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

1 Table modified from Schünemann H, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al. ATS Documents
2 Development and Implementation Committee. An official ATS statement: Grading the quality of evidence and
3 strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006
4 Sep 1;174(5):605–14.